



NOTES

GENETIC MUTATIONS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Permanent alterations of DNA sequence → clinically significant syndrome
- Germ cell mutations inherited
- Somatic cell mutations due to environmental factors (e.g. radiation)
- *Physiologic, pathologic processes*: evolution, immune system development, cancer

Inheritance patterns

- *Autosomal dominant*: one genetic copy mutated
- *Autosomal recessive*: both genetic copies mutated
- *X-linked (dominant/recessive)*: mutation in X chromosome; no transmission from father to son; individuals who are biologically male more frequently/severely affected
- *Y-linked*: mutation in Y chromosome; passed from father to son
- *Codominant*: two alleles affect same trait (e.g. ABO blood group)
- *Mitochondrial*: mutation in mitochondrial DNA; maternal inheritance

CAUSES

Error during DNA replication

- *Point mutation within coding sequences*: substitution of single base; may occur as transition (e.g. purine → purine)/transversion (e.g. purine → pyrimidine)
 - *Silent*: codes same amino acid, no phenotypic change
 - *Missense*: codes different amino acid, may cause phenotypic change (e.g. sickle cell anemia)
 - *Nonsense*: early stop codon, produces nonfunctional protein, may cause

phenotypic change (e.g. adrenal gland hyperplasia)

- *Point mutation within noncoding sequences*: mutation of promoter/enhancer sequences → reduced/abolished transcription
- *Deletion*: removal of bases
- *Insertion*: addition of bases
 - *Splice site mutation*: altered splicing of mRNA
 - *Frameshift*: shifted reading frame
- *Trinucleotide-repeat mutation*: ↑ trinucleotide repeats
- *Disorders of imprinting*: one gene copy silenced by methylation (e.g. Prader-Willis syndrome)

TYPES

Mendelian disorder

- Single gene mutation, large effects

Chromosomal disorder

- *Numerical*: insertion/deletion of entire chromosome (e.g. trisomies, aneuploidies)
- *Structural*: change in genetic sequence

Complex multigenic disorder (polymorphism)

- Genes increase risk of disease, no gene capable of causing disease on own (e.g. hypertension, diabetes mellitus)

RISK FACTORS

- Parental genetic defect
- Exposure to radiation, carcinogens

COMPLICATIONS

- Spontaneous abortion; severe organ defects (e.g. tetralogy of Fallot, renal dysplasia); visual/hearing disturbances;

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growth deficiency; intellectual disability; cancer

SIGNS & SYMPTOMS

- Abnormal physical features
- Organ defect-related signs/symptoms

DIAGNOSIS

DIAGNOSTIC IMAGING

X-ray, CT scan

- Evidence of organ defects (e.g. fibrous dysplasia, cardiac malformations)

LAB RESULTS

- Altered blood tests, hormones, liver enzymes

OTHER DIAGNOSTICS

- History, physical examination
- Genetic tests

TREATMENT

SURGERY

- Surgical repair of significant defects

ALAGILLE SYNDROME (ALGS)

osms.it/alagille-syndrome

PATHOLOGY & CAUSES

- Autosomal dominant disorder → liver, skeletal, ocular, cardiac, renal defects
- AKA arteriohepatic dysplasia, Alagille–Watson syndrome
- Variable penetrance; severity related to size of deletion
- Sometimes associated with somatic/germline mosaicism
- Individuals susceptible to additional mutations

CAUSES

- Mutation/deletion related to notch signalling pathway (involved in angiogenesis, cell proliferation, differentiation)
 - 95% involve *JAG1* gene (chromosome 20p12)
 - *NOTCH2* gene (chromosome 1p.13); related to renal malformations
- Results in absence of intrahepatic bile ducts → ↑ risk of progressive liver disease → chronically elevated bilirubin, cholesterol

COMPLICATIONS

- Malabsorption
- Pancreatic insufficiency
- Abnormal vertebral segmentation
- Vascular anomalies (e.g. basilar artery aneurysm; ↑ risk of intracranial bleeding)

Liver

- Chronic cholestasis (95%), cirrhosis, liver failure

Cardiac

- Peripheral pulmonary artery stenosis, tetralogy of Fallot

Ocular

- Shallow anterior chamber, keratoconus, embryotoxon (prominent Schwalbe's ring), Axenfeld anomaly (embryotoxon + attached iris strands), pigmentary retinopathy, cataracts

Renal

- Dysplasia, renal tubular acidosis

SIGNS & SYMPTOMS

- Intellectual disability, learning difficulties
- Hepatosplenomegaly

Cholestasis

- Jaundice, pruritus, xanthomas (cholesterol deposits in skin)

Facial features

- Triangular face, prominent forehead, hypertelorism (widely-spaced eyes), deep-set eyes, upslanting eyelids, long nose with bulbous tip, large ears, prominent mandible, pointed chin; more prominent with age

Growth deficiency

- Short stature

DIAGNOSIS

DIAGNOSTIC IMAGING

Spinal X-ray

- Butterfly-shaped vertebrae, hemivertebrae, spina bifida occulta

Abdominal ultrasound

- **Kidneys:** small, echogenic, presence of cysts, ureteropelvic obstruction

LAB RESULTS

- ↑ bilirubin (total, conjugated), ↑ liver enzymes, ↑ cholesterol
- **Liver biopsy:** intrahepatic bile duct paucity, portal inflammation

OTHER DIAGNOSTICS

- History, clinical examination
- Genetic tests

TREATMENT

MEDICATIONS

- **Choleretic agents:** ursodeoxycholic acid + cholestyramine/rifampin/naltrexone

SURGERY

- Biliary diversion/liver transplantation
- Heart defect surgical repair

OTHER INTERVENTIONS

- Nutritional support

MCCUNE–ALBRIGHT SYNDROME

osms.it/mccune-albright_syndrome

PATHOLOGY & CAUSES

- Genetic disorder characterized by fibrous dysplasia (FD), endocrinopathy, **unilateral café-au-lait skin spots**
- Occurs most commonly in skull base/proximal femur; most lesions appear < age 15
- **External beam radiotherapy:** ↑ risk of malignant transformation
- More common among individuals who are biologically female

- Post zygotic mutation in GNAS1 gene (20q.13.1-13.2)
 - Encodes Gs alpha protein → **G protein/** cAMP/adenylate cyclase signaling pathway
- **Somatic mosaicism:** some somatic cells mutated

COMPLICATIONS

- Pathologic fractures; osteosarcoma; osteomalacia; visual/hearing disturbances (due to nerve compression); severe pain; scoliosis; ovarian cysts; acromegaly,

gigantism; Mazabraud syndrome (fibrous dysplasia + intra/juxtamuscular myxoma); liver disease; higher risk of thyroid, testicular, breast cancer

SIGNS & SYMPTOMS

Clinical triad

- Bone fibrous dysplasia
 - Limp, pain, dysmorphism
- Hyperfunctioning endocrinopathy
 - **Hyperthyroidism**: change in appetite, insomnia, fatigue, palpitations
 - **Cushing's syndrome**: moon facies, plethora, hirsutism
 - **Growth hormone (GH) excess**: enlarged facial/body features, excessive sweating, thickened skin
 - **Renal phosphate wasting**: usually asymptomatic; weakness, pain, altered mental status
 - **Precocious puberty**: early vaginal bleeding, breast development in individuals who are biologically female; early testicular/penile enlargement, scrotal rugae, body odor, pubic/axillary hair, sexual behaviour in individuals who are biologically male
- Café-au-lait skin spots
 - Brown macules, **irregular borders** ("coast of Maine"); mostly on lower back, buttocks

DIAGNOSIS

DIAGNOSTIC IMAGING

X-ray, radionuclide bone scan

- **Long bones**: expansile, lytic lesions; endosteal scalloping (focal resorption of cortex inner layer), cortex thinning, "ground-glass" appearance of medulla; epiphysis usually spared
 - **Proximal femur**: "shepherd's crook" malformation
- **Skull**: sclerotic lesions, "ground-glass" appearance, cyst-like lesions

Thyroid ultrasound

- Presence of cystic areas

LAB RESULTS

Hyperthyroidism

- ↓ thyroid stimulating hormone (TSH), ↑ triiodothyronine (T3)

GH excess

- ↑ GH, ↑ prolactin

Cushing's syndrome

- ↑ 24-hour urinary free cortisol

Renal phosphate wasting

- ↑ urinary phosphate, ↓ serum phosphate

Precocious puberty

- ↑ testosterone/estradiol, ↓ luteinizing hormone (LH), ↓ follicle-stimulating hormone (FSH)

Bone tissue biopsy

- Absence of lamellation pattern, "Chinese writing" pattern, areas of unmineralized osteoid

OTHER DIAGNOSTICS

- History, physical examination
- Genetic tests (e.g. polymerase chain reaction, next-generation sequencing)

TREATMENT

MEDICATIONS

- Bisphosphonate treatment for pain management (no effect on disease progression)
- Medication for endocrine disorders (e.g. gonadotropin releasing hormone analogues, tamoxifen, thionamides)

SURGERY

- Surgical management of fibrous dysplasia (e.g. intramedullary devices, bone grafting)

OTHER INTERVENTIONS

- Physical exercise (e.g. cycling, swimming)
 - ↑ bone support → ↓ fracture risk

PRIMARY CILIARY DYSKINESIA

osms.it/primary-ciliary-dyskinesia

PATHOLOGY & CAUSES

- Congenital disease; defect in cilia motility → impaired mucociliary clearance, decreased fertility
- AKA immotile-cilia syndrome
- Affects cilia of respiratory tract, fallopian tubes, sperm flagella
- **Inheritance pattern:** autosomal recessive

CAUSES

- Defect in proteins of cilia structure → absent/altered motion (e.g. clockwise rotation)
- Genetic mutations
 - *DNAH5*, *DNAI1*: encode axonemal outer dynein arms
 - *RSPH4A*, *RSPH9*: encode radial spokes

COMPLICATIONS

- Chronic sinusitis; Kartagener's syndrome (situs inversus, chronic sinusitis, and bronchiectasis); hydrocephalus; transposition of great vessels; epispadias; pectus excavatum; chronic secretory otitis media; conductive hearing loss

SIGNS & SYMPTOMS

- **Recurrent upper/lower respiratory tract infections:** chronic cough, mucopurulent sputum; symptoms increase during course of day
- **Newborns:** present with mild respiratory distress (tachypnea, mild hypoxemia)
- **Bronchiectasis:** crackles, wheezes
 - **Exacerbation:** dark sputum, dyspnea, pleuritic pain
- **Rhinosinusitis:** runny nose, constant congestion, nasal polyps, altered sense of smell
- Fatigue, headaches

- Infertility
- ↓ aerobic fitness

DIAGNOSIS

DIAGNOSTIC IMAGING

Chest X-ray, CT scan

- Pulmonary hyperinflation, peribronchial thickening, atelectasis, bronchiectasis; situs inversus

LAB RESULTS

- Reduced/absent nasal nitric oxide (also present in some cases of cystic fibrosis)

Cell culture

- **Inferior concha epithelium:** tissue culture → cilia shed → emergence of new, immotile cilia → diagnosis confirmation

OTHER DIAGNOSTICS

- **Spirometry:** obstructive pattern
- Genetic tests

Ciliary motion, ultrastructure

- **High speed video microscopy analysis (HSVA):** live examination of respiratory epithelial cells; after air-liquid interface/cooling → assessment of motion pattern, beat frequency
- **Transmission electron microscopy (TEM):** observation of ciliary ultrastructure defects

TREATMENT

MEDICATIONS

- **Bronchiectasis**
- Antibiotics, airway hydration (e.g. nebulized hypertonic saline), mucolytic agents

Chronic rhinitis

- Nasal saline lavage + intranasal glucocorticoids

SURGERY

Chronic rhinitis

- Polyp removal

OTHER INTERVENTIONS

- Smoking cessation
- Pneumococcus, influenza vaccination

Bronchiectasis

- Daily chest physiotherapy

TREACHER COLLINS SYNDROME

osms.it/treacher-collins-syndrome

PATHOLOGY & CAUSES

- Severe genetic disorder of craniofacial development
- AKA mandibulofacial dysostosis, Franceschetti–Zwahlen–Klein syndrome
- **Inheritance pattern:** autosomal dominant, variable penetrance; 60% spontaneous

CAUSES

- TCOF1 gene mutation (chromosome 5q32) → treacle protein (ribosome biogenesis regulator) insufficiency → neuroepithelial cell apoptosis → ↓ neural crest cells → first, second branchial arch anomalies → cranioskeletal hypoplasia
- **Other genetic mutations:** POLR1C (6q21.2), POLR1D (13q12.2); involved in ribosome biogenesis

COMPLICATIONS

- Perinatal death; bilateral conductive hearing loss; speech problems; airway compromise; feeding difficulties; visual loss; brachycephaly; choanal atresia; congenital heart defects; intellectual disability; renal malformation

SIGNS & SYMPTOMS

- **Facial bone hypoplasia** (esp. mandible, zygomatic bone): retrognathia, sunken cheeks
- Facial asymmetry
- Projection of scalp hair to lateral cheek
- **Dental:** high/arched/cleft palate; malocclusion, tooth agenesis, enamel opacities
- **Ocular:** downslanting eyelids, lower eyelid coloboma, paucity of eyelashes medial to notch, hypertelorism (widely spaced eyes)
- Malformation of external ear, external auditory canals, middle ear ossicles

DIAGNOSIS

DIAGNOSTIC IMAGING

Cranial X-ray, orthopantomogram, CT scan

- Facial bone hypoplasia, altered middle ear ossicles, external auditory canal stenosis

OTHER DIAGNOSTICS

- History, clinical examination
- **Prenatal:** amniocentesis, chorionic villus sampling

TREATMENT

SURGERY

- Reconstructive surgery
- Tracheostomy (severe airway obstruction at birth)
- Glossopexy (tongue-lip adhesion)
- Corrective surgery for cleft lip/palate/choanal atresia
- Gastrostomy tube placement

OTHER INTERVENTIONS

- Supportive treatments (e.g. hearing aid, speech therapy)



Figure 25.1 The face of a female child with Treacher Collins syndrome.